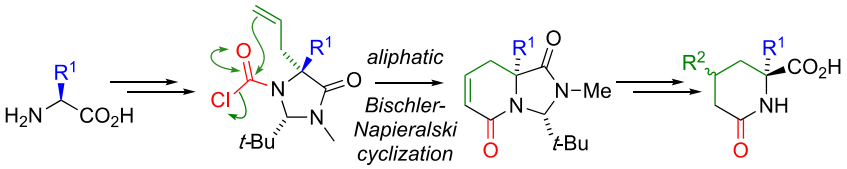
Amer, M. M., Olaizola, O., Carter, J., Abas, H., & Clayden, J. (2020). An Aliphatic Bischler–Napieralski Reaction: Dihydropyridones by Cyclocarbonylation of 3-Allylimidazolidin-4-ones. *Organic Letters*, *22*(1), 253-256. https://doi.org/10.1021/acs.orglett.9b04250

An Aliphatic Bischler-Napieralski reaction: Dihydropyridones by Cyclocarbonylation of 3-Allylimidazolidin-4-ones

Mostafa M. Amer, Olatz Olaizola, Jennifer Carter, Hossay Abas, and Jonathan Clayden*

School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK

Supporting Information Placeholder



ABSTRACT: The *N*-chloroformylimidazolidinone derivative of enantiopure L-alanine was deprotonated to form an enolate and functionalized with a series of allylic halides. Treatment of the resulting carbamoyl chlorides with potassium iodide led to cyclisation of the allylic substituent onto the carbonyl group in an intramolecular aliphatic Friedel Crafts-type acylation that corresponds to an aliphatic Bischler-Napieralski reaction. The product 3,4-dihydropyridinones were amenable to further functionalization, and finally hydrolysis, to deliver a series of enantioenriched pipecolic acid derivatives.

The dihydropyridin-2-one scaffold and its derivatives are found embedded in a number of naturally occurring alkaloids and constitutes the core of many other biologically relevant compounds. Examples include the small molecule direct thrombin inhibitor argatroban, which acts as an anticoagulant.[1,2] Dutasteride is a 5α-reductase inhibitor, approved for the treatment of enlarged prostate.[3,4] Setrobuvir is an experimental drug candidate (Phase II) which is used alongside interferon for the treatment of hepatitis C patients.[5] Piperlongumine belongs to the *Piperaceae* family of natural products, which are widely known for their anti-cancer properties (Figure 1).[6,7]

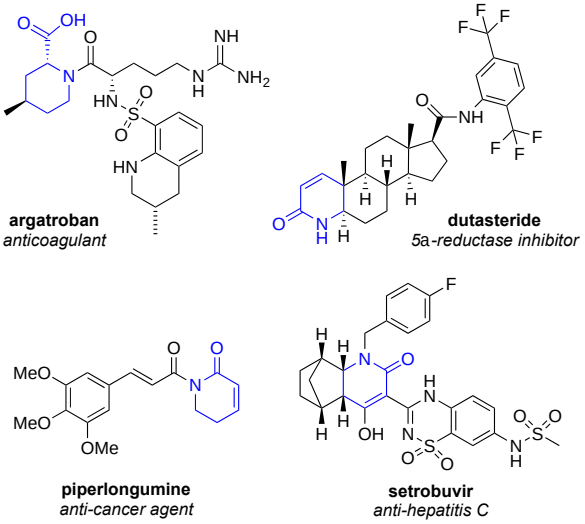
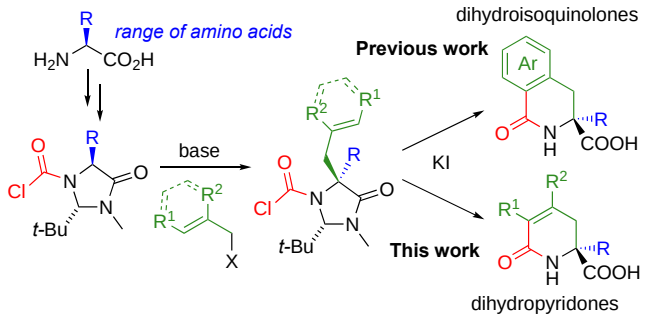


Figure 1. Bioactive 4,5-dihydropyridin-2-one derivatives

Recently reported connective syntheses of the dihydropyridinone ring system have involved intramolecular attack of enamines on Michael acceptors[8] or epoxides,[9] cycloadditions of imines,[10] and carbamoylation of alkenes.[11] We recently reported a synthesis of the benzo-fused analogues of 3,4-dihydropyridin-2-ones, namely 3,4-dihydroisoquinolinones, by an unusual version of the Bischler-Napieralski cyclisation entailing the intramolecular KI-promoted Friedel-Crafts acylation of *N*-chloroformylimidazolidinones (Scheme 1).[12] The starting materials for these reactions, imidazolidinone-derived carbamoyl chlorides carrying a 3-benzyl substituent, were formed diastereoselectively either directly from aromatic amino acids (for example, L-Phe)[12] or by stereoselective benzylation[13] of the stable enolates[14] of their *N*-chloroformyl substituted precursors.[15]



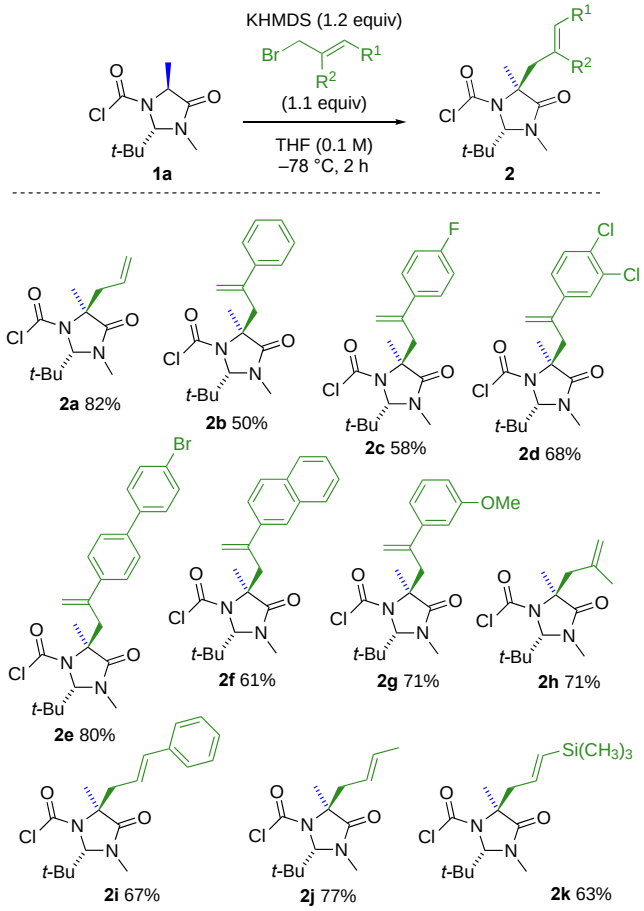
Scheme 1. Dihydroisoquinolones by cyclization of amino acid-derived *N*-chloroformylimidazolidones

We now show that 3,4-dihydropyridin-2-ones may likewise be formed by intramolecular Friedel-Crafts reaction, from imidazolidinones bearing 3-allyl substituents. This aliphatic

version[11] of the Bischler-Napieralski reaction[16,17] forms versatile products that may be used as precursors to functionalized saturated or unsaturated pipecolic acid derivatives bearing a quaternary centre α to nitrogen (Scheme 1).

The work started with the enantiopure *N*-chloroformylimidazolidinone derivative **1a**, formed as a single *trans* diastereoisomer[12] from L-Ala. The potassium enolate of this heterocycle, formed by treatment with KHMDS, is stable enough to be trapped with allylic electrophiles at −78 °C.[14] Better yields were obtained by shortening the interval between the addition of the base and the electrophile (see SI for optimization table), and the optimal conditions involved treating *N*-chloroformylimidazolidinone **1a** with KHMDS (1.2 eq) and stirring for 2 min before adding the electrophile, which was left to react for 2 h at −78 °C.

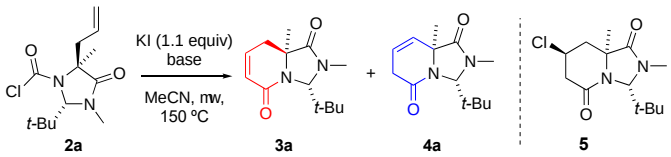
The enolate reacted successfully with allyl bromides bearing a variety of functional groups and substitution patterns (*i.e.* where R^1 or $R^2 \neq H$). Using these optimized reaction conditions we synthesized a range of enantiopure *N*-chloroformylimidazolidinones **2a-2k** carrying a variety of differently substituted allyl substituents (Scheme 2) in good to excellent yields. As observed previously, the addition of the electrophile was fully diastereoselective (none of the *cis*-allylated diastereomer was observed by ^{1}H NMR), with nOe confirming that the electrophile approaches *anti* to the bulky *tert*-butyl group.



Scheme 2. Diastereoselective allylation

Intramolecular electrophilic attack of the *N*-chloroformyl group onto the alkene was induced by treatment with KI, which we assume generates a transient acyl iodide intermediate.[18] Using 3-allyl *N*-chloroformylimidazolidinone **2a** as a model substrate (Table 1) we found that cyclization was complete after 2 h in the presence of 1.1 equiv 2,6-lutidine (entry 1), but gave a mixture of alkene regioisomers: the conjugated product **3a** and unconjugated product **4a** formed in a 41:59 ratio. The products were separated by flash chromatography, and their structures confirmed by X-ray crystallography (Figure 2).[19] Alternative activation of the chloroformyl group by complexation to $AlCl_3$ gave a single diastereoisomer of the chlorinated product **5** in significant amounts (entry 2).

Table 1. Optimization of the cyclocarbonylation



entry	Base (equiv)	Crude ratio (**3a**:**4a**)	Isolated yield **3a** (%)	Isolate yield **4a** (%)[c]
1	2,6-Lutidine (1.1)	41:59	39	50
2	[$AlCl_3$][d]	–	46	22[e]
3	DBU (1.1)	63:37	34	21
4	DBU (3.0)	77:23	19	19
5[a]	2,6-Lutidine (1.1) then DBU (5)	85:15	43	-
6[b]	2,6-Lutidine (1.1) then DBU (5)	85:15	39	-
7[c]	2,6-Lutidine (1.1) then DBU (3)	-	45[f] + 43[g]	50[f]

[a]Treated with DBU (2 h, 150 °C) before work-up. [b]Treated with DBU (2 h, 150 °C) after work-up. [c]Products separated and isolated; **4a** then treated with DBU (2 h, 150 °C). [d]No base used; $AlCl_3$ in CH_2Cl_2 used instead of KI. [e]Yield of **5**. [f]Yield formed in initial cyclization. [g]Further material isolated after isomerization from **4a**.

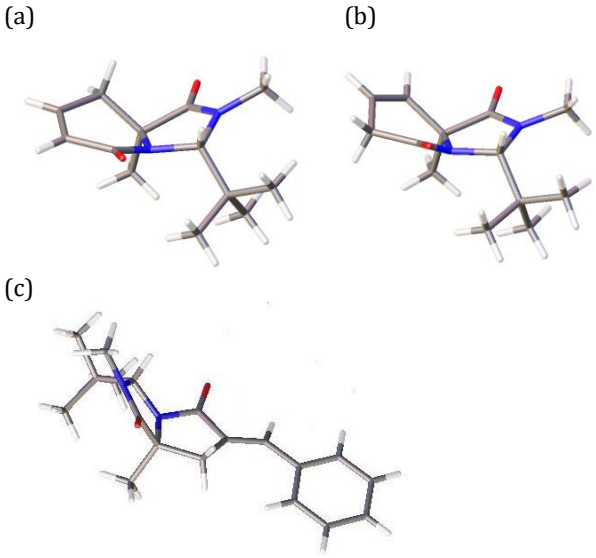
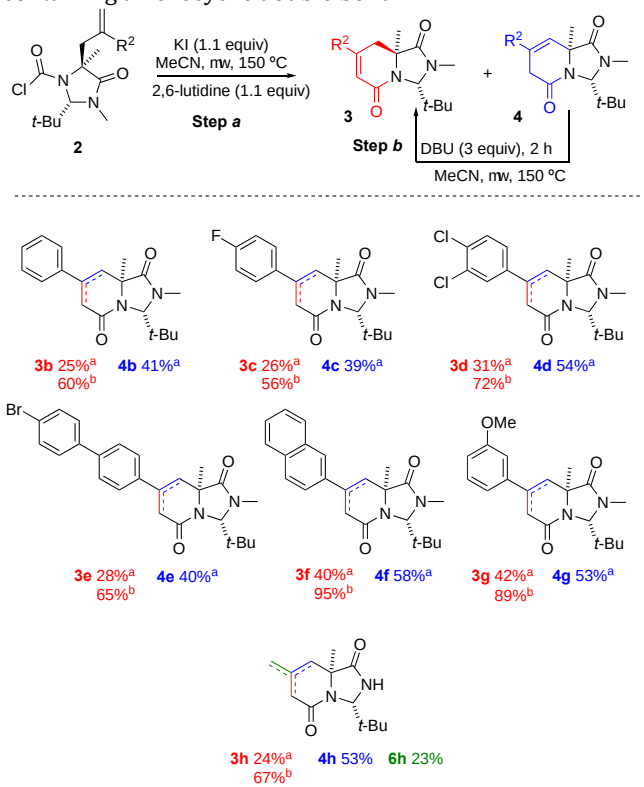


Figure 2: X-ray crystal structures of (a) **3a**; (b) **4a**; (c) *E*-**7i**

Looking to improve the isolated yield of the more useful conjugated product **3a**, we explored the reaction in the presence of alternative bases. Donohoe *et al.* reported the use of DBU to isomerize an unconjugated double bond into conjugation in a related heterocycle.[20] Using DBU in place of 2,6-lutidine (entries 3 and 4) improved the proportion of **3a** in the crude material to 63-77%, but isolated yields were moderate. More satisfactory was a stepwise protocol (entry 5) in which the starting material was treated with KI and 2,6-lutidine to induce cyclization, followed by DBU to effect isomerization to **3a**, either with or without work-up between the steps (entries 6, 7). This procedure gave solely **3a**, but still in relatively poor yield. The optimal procedure turned out to be the separation of **4a** from **3a**, followed by isomerization of the isolated **4a** to **3a** in a separate step, which gave an overall combined yield of 88% **3a** (entry 7).

The scope of the intramolecular aliphatic Friedel Crafts acyation, which amounts to an aliphatic equivalent of the Bischler-Napieralski cyclization, was explored by cyclization of imidazolidinones **2b-2h**. These substrates, bearing 2-substituted allyl groups, cyclized to give chromatographically separable mixtures of regioisomers **3** and **4** in ratios comparable to those seen with **2a**. As before, treatment with DBU returned good yields of the conjugated products **3b-3g** (Scheme 3). Imidazolidinone **2h**, with a 2-methallyl substituent, gave (in addition to **3h** and **4h**) a third regioisomer **6h** containing an exocyclic double bond.

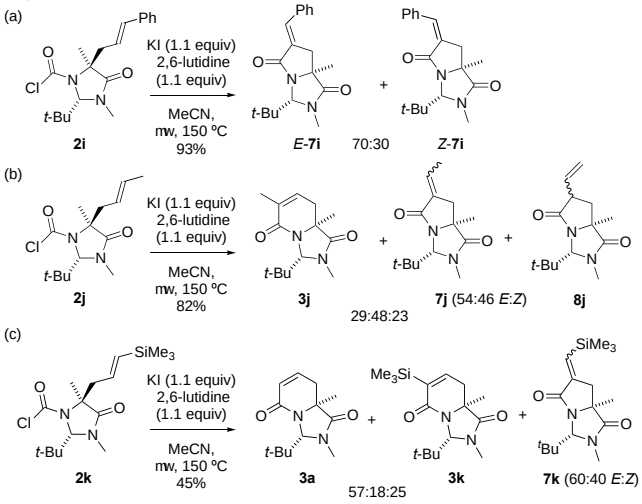


Scheme 3. Scope of the cyclocarbonylation. [a]Yield isolated after step *a*. [b]Combined isolated yield from step *a* and step *b*.

Substrates in which the allyl group was substituted at the terminal position also gave a more diverse range of outcomes (Scheme 4). Cinnamyl-substituted **2i** (Scheme 4a), underwent cyclisation to form a five-membered ring, presumably as a result of the more stable benzylic cation that forms. Two alkene stereoisomers *E*- and *Z*-**7i** were formed, their geometry being assigned from the X-ray crystal structure of the *E* isomer (Figure 2c).

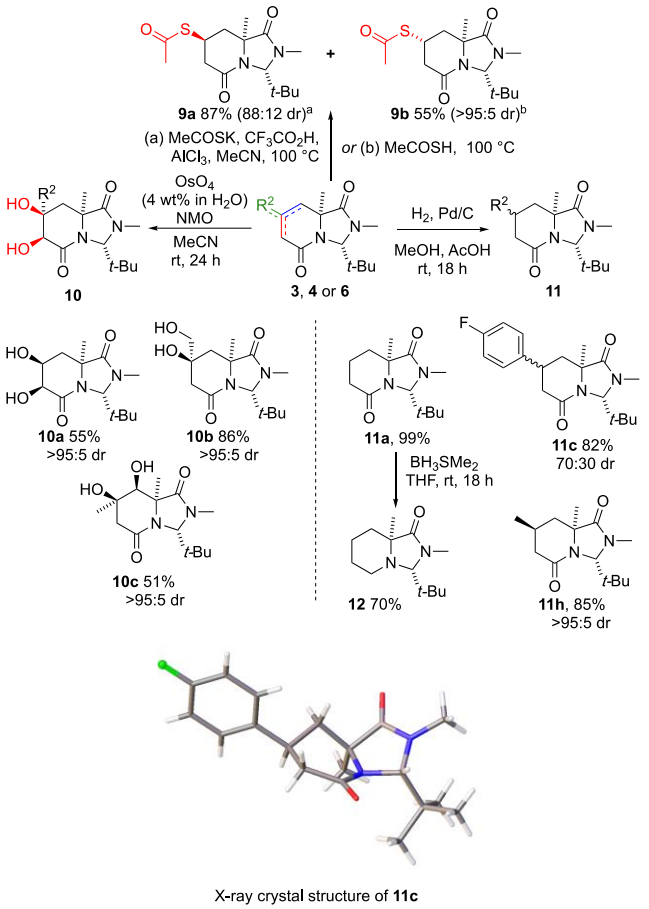
The crotyl substituent of **2j** gave, under the same conditions, both 6- (**3j**) and 5-membered cyclized products (Scheme 4b), with the 5-membered products being generated as a mixture of double bond isomers **7j** and **8j**.

Attempts were made to bias this cyclization towards the six-membered ring **3** by incorporation of a silyl directing group in precursor **2k**. 6-ring selectivity improved as a result, with **3a** becoming the major product, but surprisingly 5-ring **7k** was still formed in significant amounts (Scheme 4c).



Scheme 4. Cyclization of terminally substituted allyl substituents.

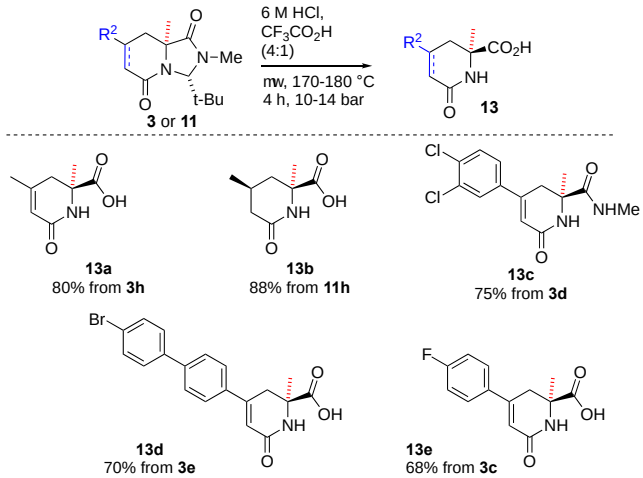
The imidazolinone-fused 3,4-dihydropyridin-3-ones **3**, **4** and **6** present a reactive electrophilic alkene within a highly stereodefined environment, and thus offer many possibilities for application in enantioselective synthesis of pyridinone and pipecolic acid derivatives through further functionalization.[21] A number of such transformations are illustrated in Scheme 5.



X-ray crystal structure of **11c**

Scheme 5. Functionalization of the dihydropyridinone scaffold. [a]Conditions (a); [b]Conditions (b). In addition, 18% dithioester formed (see SI).

Conjugate addition of thioacetate to the unsaturated alkene **3a** gave diastereoselectively the thioesters **9a** and **9b** with the major diastereoisomer depending on the conditions used. Dihydroxylation of **3a**, **4h** or **6h** gave the diols **10** highly diastereoselectively by functionalization of the endo face of the bicycle, anti to the ring junction methyl group and the *tert*-butyl substituent. Hydrogenation of **3a**, **3c** and **3h** provides pipecolic acid derivatives **11**. Further chemoselective reduction of **11a** gave pipecolic acid derivative **12**. Removal of the directing imidazolidinone motif to reveal the parent ring systems was achieved by acid-catalyzed hydrolysis to the products **13a-13e** (Scheme 6), allowing the formation of a range of enantiopure lactams carrying fully substituted stereogenic centres.



Scheme 6. Hydrolysis to give pipecolic acid derivatives.

Overall, the method makes further use of the versatile amino-acid derived enantiopure *N*-chloroformylimidazolidinones – both their stability towards base and enolate generation, and their intramolecular electrophilicity towards carbon nucleophiles on activation by iodide. By providing a route to enantiopure 3,4-dihydropyridinones, it enables a useful and potentially highly versatile route to pharmaceutically relevant substituted derivatives of pipecolic acid.

Supporting Information

The supporting information contains full experimental details and spectroscopic characterization of all new compounds. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

*E-mail: j.clayden@bristol.ac.uk.

ACKNOWLEDGMENT

This work was supported by the Presidential Leadership Programme of Egypt, the European Research Council (AdG ROCOCO), and the EPSRC.

REFERENCES

1. Dhillon, S. *Am. J. Cardiovasc. Drugs* **2009**, *9*, 261.
2. Di Nisio, M.; Middeldorp, S.; Büller, H. R. *N. Engl. J. Med.* **2005**, *353*, 1028.
3. Satyanarayana, K.; Srinivas, K.; Himabindu, V.; Reddy, G. M. *Org. Process Res. Dev.* **2007**, *11*, 842.
4. Szychowski, J.; Truchon, J.-F. O.; Bennani, Y. L. *J. Med. Chem* **2014**, *57*, 9292.
5. Jensen, D. M.; Brunda, M.; Elston, R.; Gane, E. J.; George, J.; Glavini, K.; Hammond, J. M.; Le Pogam, S.; Nájera, I.; Passe, S.; Piekarska A.; *Liver Int.* **2016**, *36*, 505.
6. Chen, W.; Lian, W.; Yuan, Y.; Li, M. *Cell Death Dis.* **2019**, *10*, 600.
7. Seo, Y. H.; Kim, J.-K.; Jun, J.-G. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5727.
8. Huang, X.; Broadbent, S.; Dvorak, C.; Zhao, S.-H. *Org. Process Res. Dev.* **2010**, *14*, 612.
9. Benhaim, C.; Bouchard, L.; Pelletier, G.; Sellstedt, J.; Kristofova, L.; Daigneault, S. *Org. Lett.* **2010**, *12*, 2008.
10. Kaasik, M.; Metsala, A.; Kaabel, S.; Kriis, K.; Järving, I.;

Kanger, T. *J. Org. Chem.* **2019**, *84*, 4294.
11. Yasui, Y.; Kakinokihara, I.; Takeda, H.; Takemoto, Y. *Synthesis (Stuttg).* **2009**, No. 23, 3989.
12. Amer, M. M.; Carrasco, A. C.; Leonard, D. J.; Ward, J. W.; Clayden, J. *Org. Lett.* **2018**, *20*, 7977; Seebach, D.; Sting, A. R.; Hoffmann, M *Angew. Chem. Int. Ed.* 1996, 35, 2708.
13. Abas, H.; Amer, M. M.; Olaizola, O.; Clayden, J. *Org. Lett.* **2019**, *21*, 1908.
14. Amer, M. M.; Abas, H.; Leonard, D. J.; Ward, J. W.; Clayden, J. *J. Org. Chem.* **2019**, *84*, 7199.
15. Leonard, D. J.; Ward, J. W.; Clayden, J. *Nature* **2018**, *562*, 105.
16. Chrzanowska, M.; Grajewska, A.; Rozwadowska, M. D. *Chem. Rev.* **2016**, *116*, 12369.
17. Chavan, S. P.; Garai, S.; Dey, C.; Gonnade, R. G. *Tetrahedron Lett.* **2013**, *54*, 5562.
18. Wakeham, R. J.; Taylor, J. E.; Bull, S. D.; Morris, J. A.; Williams, J. M. J. *Org. Lett.* **2013**, *15*, 702.
19. X-ray crystallography data has been deposited with the Cambridge Crystallographic Data. Deposition numbers **3a**, 1967823; **4a**, 1967824; *E*-**7i**, 1967826; **11c**, 1967825.
20. Donohoe, T. J.; Connolly, M. J.; Walton, L. *Org. Lett.* **2009**, *11*, 5562.
21. Meyers, A. I.; Seefeld, M. A.; Lefker, B. A. *J. Org. Chem.* **1996**, *61*, 5712.